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## *THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE*

## *THE INFLUENCE OF PARASITISM ON THE HOST*[1]

THE line of development within the field of zoological research has shown a distinct tendency within recent years to move in the direction of biological study, to view the organism as a living thing and to seek an explanation for the various problems of life which present themselves in connection with it. One of the earliest phases of biological study found its origin in the condition presented by parasitism. The class of Helminthes, or intestinal worms, of the earliest authors, was seen early in the course of morphological study to be unwarranted as a systematic grouping. The animals included under the term were not those which were in any genetic sense related to each other. Like the earlier designations of land animals and water animals, these forms were grouped together by virtue of similarity in conditions of existence. The term is accordingly a biological one and its purely biological significance was stoutly maintained as early as 1827, by the great embryologist, Carl Ernst von Baer, and by F. S. Leuckart. The idea received finally due acceptance through the efforts of Carl Vogt, who dissociated the earlier group and united its subdivisions with those free living animals to which they were most closely morphologically con-

[1] Address of the vice-president and chairman of Section F—Zoology, American Association for the Advancement of Science, New York meeting, December, 1906.

nected. Even thus early it was apparent that parasitic animals were derived from free living forms, that they were in fact but degraded members of the same groups; in some cases with such little modification in structure that their affinities were recognized at a glance, in other cases, however, the excessive modification had carried the parasitic form very far from the ancestral type, and yet the existence of a large number of intermediate stages suggested at once that these changes had been gradual.

In spite of the fact that these studies were among the very earliest of biological investigations, it appears that the reciprocal influence has rather generally escaped discussion. It is my desire, accordingly, in so far as may be practicable within the limits of time and space of a single address, to set before you the main facts in connection with this other side of parasitism—the influences which are exerted upon the host animal, the changes wrought in it, and the part they play in the problems of general biology. There is a vast amount of information and detail regarding individual species; and in some cases the relations have been investigated with great care from the standpoint not only of the morphologist and of the physiologist, but even also from that of the chemist; but in the main these observations stand as isolated and unrelated facts. I have neither the knowledge nor the ability to bring them all together into a concrete whole, but there are certain general headings under which it is possible without especial effort or explanation to group some of the phenomena, while others must wait for better knowledge or clearer perception than I possess before they can be included in any generalizations.

In rough fashion it is the custom to class parasites as harmful and harmless. The harmful forms induce pathological changes, stand in some definite relation to disease and become, accordingly, of prime importance to the investigator in medical fields. The other forms, while spoken of as harmless or without effect, certainly should not be classed as exercising none. With the exception of certain striking instances, especially among those forms which parasitize man, the effects of parasitism are almost unknown, hence they are largely ignored. In the course of time opinions on this matter have changed radically. As I have said in another paper:

"In the belief of the medical profession two hundred years ago there was no disease, real or imaginary, which was not due to the presence and effect of some kind of parasite. Each ailment had its particular 'worm' in its characteristic location. This was a direct result of the endeavor to reduce every malady to some definite cause, and from a joining of the unknown sickness with the parasites, of which they knew as little. Under the influence of study and of increase in knowledge regarding the parasites, such a theory was seen to be untenable, and the movement in the opposite direction began—a tendency which may be said by this time to have passed its height. In fact, there has prevailed during recent years among the medical men of this country an exaggerated idea of the unimportance of human parasites." This must give way to a proper conception of the pathological significance of these organisms, based upon careful investigations of their actual influence upon the host.

Yet there are some parasites of which it may fairly be said that even careful study has failed to show any manner in which they affect the host. Thus Looss records of a distome (*Heterophyes*) commonly found in the human alimentary canal among Egyptian laborers, that, although present in considerable numbers, most careful scrutiny fails to disclose any influence which it exerts upon the host. This is

traceable to the fact that it neither burrows into nor feeds upon the mucous lining of the canal, but contents itself with taking its food from the partially digested contents of the intestine. Inasmuch as the organism is very small, this is evidently a negligible factor in the economy of the host; but even here, as I shall show later, there is the possibility that under some circumstances the organism may become a menace. Again, *Filaria loa,* the African eye worm, lives for many years in the connective tissue of the human body, wandering from point to point, often not far below the skin. In the course of its migrations it does apparently no injury to the host, who is indeed unconscious of its presence until it happens to come into the connective tissue over the surface of the eyeball. Here it appeals to the sense of sight, and from here it has most frequently been extracted. But in this case again there are swellings which appear from time to time on the surface of the body and which are believed by some to be due in one way or other to this parasite.

In the group of indifferent bodies we must also include many, if not all, of the resting forms, those which, like the bladder worms, or the young trichinæ, are encysted at a given point and which consequently are not to any appreciable extent absorbing nutrition or producing toxic materials. The encapsulated trichina is but a grain of sand, the encysted bladder worm no more than a globule of fat in the tissue. During its entire life in the body the guinea worm does not seem to exercise any influence whatever upon the host organism until the female appears at the surface and is desirous of securing an opening through which it may discharge the young into the outer world, where they will find conditions for further existence.

These few preliminary statements have paved the way for a somewhat clearer general idea of the factors which determine the degree of influence exerted by the parasite on its host, and the first is evidently the numerical factor. Commonly, the single parasite leaves no effect; it is the multiplication of parasites which is to be feared. Evidently this multiplication will be most serious when it takes place within the host and leads directly to a multiple infection. This is known among the protozoa, where, in at least one host, there is usually a recurrence of generations of the same type, and this feature is so characteristic that Doflein designates this cycle of the life history as the multiplicative cycle, defining its purpose as being to achieve the multiple infection of the host. There are also some worms among the Nematodes in which the same thing takes place and by virtue of which the infection of the alimentary canal is enormously increased in direct fashion.

Among most metazoan parasites, however, including all Trematodes, Cestodes and some Nematodes, such is not the case. The eggs of the individual must be transported to the outer world before they can carry out their development, and they reach a new host after a more or less complicated life history which may involve alternation of generations and parasitism in one or more intermediate hosts, so that when the stage comes in which the infection of the first species is possible, it is very unlikely that the original individual will be reinfected. Among such parasites the effects from a single individual are not serious and the real danger lies in a multiple infection through the increase in numbers which such a species often experiences in the intermediate host, or within a limited area in the outer world, so that by the taking in of a single external object a large number of parasites may be introduced. Where alternations of generations exist the dangers of the parasitic existence are so great

that the number of parasites is kept down. Yet under a favorable combination of circumstances the numbers of a given parasite may be enormously increased and with this the dangers from the species also enhanced.

Naturally, immediately related to the factor of numbers is the question of comparative size. In a general way the effects of a parasite are related to its mass as compared with that of the host, and this will be clearly manifest in the subsequent discussion. From a special point of view, however, this is absolutely untrue and the secondary effects of an individual species may be out of all proportion to its size. This will also receive more detailed discussion at a later point.

Evidently, both of the factors which have just been mentioned are largely relative and distinctly such with regard to the seat of the injury, *i. e.*, the organ of the body which is attacked; thus a parasite may be quite harmless if located in connective tissue, or between the muscle fibers, while if the same specimen were to be located in the brain or in the eye its effect would be very serious. A small organism would pass entirely unnoticed in the alimentary canal, but in the heart or blood vessel, it might well cause serious disturbances, or under certain conditions even the death of the host, so that the pathogenic significance of a parasite depends essentially upon its location.

The effects of a parasite on the host may be roughly classified as mechanical, morphological and physiological. To be sure, a sharp separation is not possible at all points and frequently the one influence involves concurrently or subsequently such as belong to another group.

Animal parasites, for the most part, produce only local changes and these are explicable on purely mechanical grounds, or they are structural or functional within limited areas. But physiological influences sometimes manifest themselves as symptoms of a general disease. Such manifestations ordinarily accompany the multiplication of the parasite within the host or at least its presence there in large numbers.

Many of the effects upon the host produced by parasites may be explained in purely mechanical fashion, and under this heading are included those which produce even some of the more complicated and far-reaching results of parasitic infection through the secondary effects which they induce.

Regarding the parasite as a passive mass, a purely inert body, it may bring about a stoppage of various passageways and thus induce serious consequences for the host. Such an occlusion of a canal may follow under perfectly normal conditions, but more frequently there is something unusual that tends to induce the condition; either that the parasite is in an abnormal location or that some factor enters into its normal habitat to aid in purely mechanical fashion in the stoppage of the passageway. Thus, the accumulation of a group of common round worms into a ball will suffice at times to occlude entirely the alimentary canal, and the worms, tangled and twisted together, stop the passage of food materials and waste. Unless the condition is accurately diagnosed and promptly alleviated by operative means, this stoppage of the canal results in the death of the host. Such has been the result in man in several cases on record and similar instances are more frequent among other hosts. But in one of the more carefully investigated cases it was found that the mass of seventy-two ascarids were inextricably tangled together by a long hair swallowed by accident and in some way twisted tighter and tighter through the contortions of the parasites.

The young sclerostomes of the horse live in the large arteries of the abdomen. Their presence in these arteries explains

the aneurisms frequent at this point, as they obstruct the vessels and raise the arterial tension behind the points where they have formed a blockade. This induces in a purely mechanical way a distension of the vessels at the region of increased pressure.

Even much more complicated changes in the host may be reduced in final analysis to a mechanical effect. In the case of the Egyptian blood fluke, the female goes into the venous plexus of the pelvis to oviposit and the oval eggs which are supplied with a rudimentary spine at one end are carried into the capillaries by the blood current and there gradually work their way through the wall of the alimentary canal, or the urinary bladder, so as to reach the cavity of the organ and to escape from the body. The large numbers of these eggs which are produced fill up the capillaries, interfere with the flow of blood, lacerate the capillary walls and tissues through which they are forced mechanically until a series of serious changes is invoked in the organs in question. The condition is even more serious when these same eggs chance to be carried about the body of the host by the circulating blood, become entangled in the capillary network at different points and constitute the foci of small emboli. Such may arise in the brain where retardation of the blood current and the resulting emboli are sources of serious danger to the host, since they give rise to brain tumors and may evoke apoplectic symptoms. The effects produced by such brain tumors of parasitic origin do not differ from those of other tumors or other foreign bodies. All of these effects are at basis mechanical and the same results would apparently be produced by any inert bodies of similar form and number.

One may go still further and call attention to the fact that in some cases it is a mass of embryos which constitute the mechanical influence at the basis of serious changes. Some of the filariæ which inhabit the connective tissue are viviparous and produce countless numbers of embryos; these are carried by the lymph and blood stream all over the body; accumulating, evidently by chance, in considerable numbers at certain points of the lymph vessels, for instance, they act mechanically to produce lymph stasis and dilation of the parts. The long-continued working of this cause will produce an enormous distension of some regions of the body, giving rise to one form of the condition which is known as elephantiasis.

Another mechanical influence of the passive parasite is traceable to the pressure which it exerts upon surrounding tissues. In so far as the parasite is stable this pressure will be constant and its effect is of minor consequence; however, whenever the parasite is in a condition of active growth the gradually increasing pressure becomes an important element to consider, but the discussion of this falls naturally under a subsequent heading.

There are certain influences which the parasite exerts that are mechanical, and still are not traceable to it as a mere inert body; they rather are determined by its activity, and yet they properly deserve consideration under this head, for the parasite, though active, is exerting a purely mechanical influence, and one might conceive of the same results following upon the movement of any inanimate object. If the parasite moves about it tends to irritate and inflame or destroy the surface upon which it lies, even though it remains relatively fixed in location and merely twists from side to side. The irritation here will be evidently local and will be due to, or at least emphasized by, the spines or other roughness of the body. It will be also increased if the parasite possesses suckers or other organs of attachment. The delicate

mucous surfaces with which the parasite usually comes in contact are of all parts of the body the most susceptible to injury in this fashion, and, as we shall see later, many parasites combine with the mechanical lacerations of tissue by movements and their hold-fast organs, a physiological influence of far-reaching import.

A complicated case which indicates the combined effects of mass and motion, with possibly additional features of a physiological character not yet well understood, is illustrated by the smaller liver flukes of the genus *Opisthorchis*. These species occur in the gall ducts of the liver and there they evoke changes which, though radical, are in general uniform for different species and hosts. As the flukes advance into the finer canals of the liver, the ducts become completely occluded. The first result is bile stasis and consequent dilation of the canal until this acquires considerable size. Both the epithelial layer and the connective tissue of its wall undergo profound modifications. The epithelium shows an active catarrhal irritation. The glands manifest considerable hypertrophy. Many new accessory ducts are formed alongside the original one. Among the secondary effects one may note that while the connective tissue proliferates actively and acquires enormous thickness, the liver tissue undergoes granular degeneration as the cells gradually atrophy, thus the functional portion of the organ is gradually replaced by inert tissue. The arrest of the bile is followed by digestive disturbances and compression of the branches of the portal vein produces venous stasis, from which follows naturally the ascites so frequently observed in the course of the malady. Now all of these modifications follow the mechanical stoppage of the duct naturally, though no doubt the effect is increased by the irritation produced by the movements of the parasites. Some investigators hold that the flukes feed upon the mucous lining of the ducts; this is true of other liver flukes, but according to my observations does not apply to *Opisthorchis*.

Parasites, however, not only carry on movements through their natural territory, but they also from time to time indulge in migrations, the causes of which are not clear, but the effects are serious in the extreme.

The extent of such abnormal migrations is well illustrated by *Ascaris lumbricoides*. This form has been known to migrate along evident pathways from the duodenum into the biliary ducts, and liver, where it has induced hepatic abscesses, or into the pancreas with like results, into the larynx and trachea with the result of suffocating the host, into the eustachian tube to emerge from the auditory canal after perforating the tympanic membrane, or even into the frontal sinuses, or the internal angle of the eye.

Such erratic parasites do not always confine themselves to normal passageways of the body. Even where the penetration of tissue is distinctly exceptional, it not infrequently happens that under some unknown stimulus the species brings itself to transgress natural limitations and to open an abnormal communication between regions otherwise entirely separated. Ascarids have perforated the intestine, penetrating the peritoneal cavity, have come out from abscesses at various points, or have been discovered on the occasion of a post-mortem in the most varied regions of the body. The liver fluke as it feeds upon the hepatic cells may chance to open a small vessel, or the lung fluke may similarly effect an entrance into the circulatory system and either be thus carried into distant and unnatural parts of the body, reappearing in abscesses, and in expansions of the eyelids, or being caught in brain tumors, which sooner or later arouse the disturbances that

naturally result from the presence of foreign bodies in that organ.

The migrations of smaller forms, even though they may be numerous, are not accompanied ordinarily by the same effects as those of larger species, since the orifices they make are sufficiently minute to close immediately after the animal and prevent the secondary effects which are due to such abnormal connections. Thus the minute embryo of tapeworms migrate from the alimentary canal to the point of encystment without influencing appreciably the host, and other larvæ migrate through the tissues with such little disturbance that unless the numbers be large the host suffers no inconvenience.

Emphasis should be laid upon the extreme importance in the economy of the host which the secondary effects exert. The abrasion and destruction of surfaces and cells and the opening of abnormal communications is not *per se* of such vital importance as the results which may follow through the admission of bacteria from the canal into the blood and tissues of the animal. It is frequently held that the uninjured mucous surface is resistant to the action of bacteria and that typhoid and cholera germs must depend to some extent upon diminished resistance, functional or structural, for their original introduction into the tissues of the body. It is certainly true that many pathogenic organisms exist in the alimentary canal without detriment to the host animal, although if permitted to pass into other parts of the body they excite immediately dangerous symptoms. The perforations of the intestinal wall by *Ascaris* and the escape of such organisms into the body cavity gives at once the conditions for a serious if not fatal peritonitis, and *Ascaris* is not alone in this respect.[2]

Examples of this can be multiplied, but one will suffice. In the etiology of appendicitis certain factors are regarded as predisposing, others are direct causes of this malady. As early as 1724 Santorini recorded the presence of worms, probably *Trichuris,* in the appendix. Numerous later authors found at necropsies *Ascaris* and trichurids in this organ, as well as calculi containing eggs of *Ascaris* and *Oxyurias.* In 1901 Metchnikoff noted that in several persons who manifested symptoms of appendicitis when microscopical examination of the feces demonstrated the eggs of *Ascaris* and of *Trichuris,* the administration of a vermifuge effected a cure. He maintained that nematodes were the cause of many cases of this disease and explained the rôle of the parasites as first a direct mechanical or chemical action on the appendix and second an indirect action by the introduction of microbes into the mucosa. Metchnikoff did not commit the error attributed to him by some authors of regarding all cases of appendicitis as of parasitic origin, but specifically stated that there are certainly appendicites of different origin. Subsequent authors furnished additional evidence of the direct or indirect action of parasites in producing appendicitis, while others, though admitting the possibility that nematodes may inoculate the intestinal mucosa with bacteria, regarded this as an inappreciable factor in

[2] Piana was the first to note that the migration of *Cysticercus pisiformis* into the liver of the rabbit could introduce bacteria. In two cases of tubercular peritonitis of dog associated with *Dioctophyme renale* in the abdominal cavity Galli Valerio advanced the view that migration of the nematode made possible the development of the bacillus or carried it into cavity. It has recently been clearly shown that the pin worm, *Oxyurias,* has burrowed into the wall of the canal and produced there microscopic ulcerations, while it seems probable that it has actually made its way through the wall into the cavity of the pelvis. This perforating action places *Oxyurias* also in the ranks of parasitic introducers of bacteria.

appendicitis since their presence in this organ constitutes a pathological rarity.[3]

Evidently in producing ulcerations of the intestinal mucosa parasites facilitate the absorption of toxins from the canal and permit the inoculation of this layer with pathogenic bacteria from the intestinal contents. They can thus be the agents of inoculation for numerous diseases. Guiart, who defends this view most strongly, believes that intestinal parasites play an important rôle in the etiology of diseases of the intestine and liver, such as insects play in the etiology of blood infections. He advances evidence to support the view from the records of both human and comparative parasitology. While recognizing fully that the infections are bacterial, he emphasizes the necessity of some inoculating agent as in a sense the most important element, since pathogenic bacteria are generally present in the alimentary canal. No one can doubt, he maintains, that Eberth's bacillus is the agent of typhoid fever, but there is reason for regarding it as innocuous if the intestine is undamaged. In a population drinking contaminated water only a few persons in reality are infected. Any intestinal parasite capable of inflicting a wound may infect the host if the bacillus is present. The infecting agent may be an Ascarid, a hook worm, a fly larva; most commonly Guiart believes it to be the whip worm (*Trichuris*) which bores into the folds of the intestinal mucosa with its attenuated anterior end. This parasite Guiart calls the lancet of inoculation and demonstrated its presence in eleven out of twelve typhoid cases in one group. It is interesting to note that in 1762 this species was looked upon as the cause of typhoid and its abundant presence was noted in many epidemics by early investigators. After having gone to the opposite extreme, scientific opinion now shows a tendency to return to its earlier position and to regard the parasite an active factor in the introduction of the disease.

This unfortunate function as introducers of bacteria is, however, not confined to intestinal parasites. The chigo, or 'jigger,' a sand flea of some tropical regions, which burrows into the feet of natives, renders its host thereby exceedingly liable to infection, which in its secondary effects in the tropical clime, makes of a trivial injury one of serious consequence. The guinea worm, which burrows through connective tissue, approaching the surface at the time when it desires to deposit its embryos and producing there small ulcers or openings to the exterior, menaces the well being of its host, not by virtue of its own activity, but through the chance for infection to which it has subjected the host.

Parasites in many cases produce morphological or structural changes in their hosts, which may be classed in general as progressive histological changes in that they lead to the accumulation of material through the multiplying of the host cells.

Billroth indicated the extremely important fact that the multiplication of epithelial cells is caused by infection with micro-organisms and it has been shown that protozoa as well as bacteria may cause infected cells to multiply. Thelohan has shown that myxobolid infection produces a proliferation of muscle cells. Hofer and Doflein ascertained that in kidney infec-

[3] Galli-Valerio has subjected a recent fatal case of appendicitis to most careful examination and finds in the contents of the perforated appendix numbers of *Oxyurias vermicularis* and eggs of *Trichuris*, while sections demonstrated numerous perforations of the mucosa made apparently by the parasites and in one case the worm still within the tissue. Neither the presence of the parasites nor the evidences of their work could have been determined without a microscopic examination, and in view of the usual lack of such examination this is sufficient answer to the objections cited above to the probable rôle of parasites in the etiology of this disease.

tion by myxobolids increased growth in the skin resulted. It is also a distance effect, if not so great, when according to Leuckart the epithelial cells in coccidial nodules of the rabbit liver increase strongly in numbers. Among the epizoa there are many which produce such growths in the epithelium. The various species of itch mites excite a proliferation of the cells until there are formed crusts or thickened masses of considerable extent in which the galleries of the mites are constructed. These proliferations are said to be due merely to the mechanical stimulus exerted by the mites, and the crusts are formed by the addition of serous exudates. Such formations are thoroughly characteristic of the work of these parasites. Less well known are other cases of the same type such as that of gall-producing copepods which infest actinia.

But such stimulation is not always purely indefinite. Parasites often produce unusual forms in the region of the host in which they reside; thus, Woodworth, examining a skull of the common skunk, found that prominent swellings in the frontal bones near the sagittal plane were due to a nematode. The bone was extremely thin and in the subjacent frontal sinus lay a nest of fifteen to twenty of these parasites. The belief was expressed that the prevalent frontal enlargements of other American Mustelidæ are probably due to the same parasite.

Perhaps the most common form of morphological change on the part of the host is the production of a cyst about the parasite. It is composed in most instances, in part at least, by the host animal, and consists in its simplest form of an enveloping mass of connective tissue. This reaction against the invasion of the parasite is found in almost all groups.

The formation of pearls appears to be due regularly, if not exclusively, to the intrusion of parasitic larvæ. The host responds to the mechanical or chemical stimulus of the in-wandering larva by producing an epithelial sac which surrounds the parasite. Such a cyst formation by the host very generally follows when a parasite settles down to enter upon a resting stage in the body of the host. But here the character of the cyst wall leads normally to the formation of a deposit of lime of the same sort as the inner lining of the mollusk shell and the larval parasite becomes the nucleus of a pearl. This stimulus to pearl formation is not given by any particular species of parasite, but is traceable even to members of different classes of animals. Thus in European mussels pearls are formed about the cercariæ of Trematodes.[4]

But in the Ceylon pearl oyster, which is more nearly related to the mussels than to the oyster, the formation of pearls is due to certain cestode larvæ which undergo a portion of their development in the tissue of the liver, gills and mantle of the pearl oyster. Of these larvæ, such as for some yet unexplained reason do not succeed in carrying out their life cycle, become immured in the center of a pearl. Shipley and Hornell, who have investigated with success these phenomena, say "economically these unpleasant little creatures are of supreme importance to the Ceylon pearl fishery, as their presence in the oyster causes the formation of the finest quality of pearl and those of the highest luster." Another economic factor may be merely noted in passing. In 1859 Kelaart called attention distinctly to the possibility of infecting other beds with the larvæ of the pearl-producing parasites in order to increase the quantity of pearls. Beds of

[4] In one case carefully elucidated by Jameson the adult fluke inhabits the eider duck and the scoter, its sporocyst occurs in the cockle, while the tailless cercaria is found in the mussel and forms the nucleus of the small, lusterless pearls of that species. Another trematode is the cause of pearl formation in the fresh-water anodons.

Ceylon pearls might thus be grown in other parts of the world. Kelaart says that the nucleus of an American pearl, drawn by Möbius, is of nearly the same form as that found in the pearl oyster of Ceylon.

It is interesting to note in comparison the record of Johnstone that in the gurnard small pearl-like bodies are found adhering to the peritoneal investment of the intestine. The concretion is made up of a great number of concentric lamellæ which seem to consist of wavy bundles of connective tissue. These structures are probably derived from *Tetrarhynchus* cysts from which the larvæ had escaped and which had then undergone calcareous degeneration.

The amount of growth may be much greater than thus far indicated and a condition among animals closely analogous to the formation of galls on plants has been observed by Nutting. In certain Alcyonaria a tunnel formed of excessively enlarged spicules is found along one side of the stem or branch. The abnormal structure is due to an annelid. Greatly enlarged polyps in another genus owe their origin to the presence of crustacea or some other form of parasite.

Continued efforts have been made to demonstrate that the extensive pathological growths found in animals are due to the stimuli exerted by minute parasitic forms. It has been shown that in plants such abnormal growths are due to the encroachments of parasites; but the effort to identify animal organisms as the cause of cancerous and other abnormal growths has in the opinion of most investigators failed to establish a case.

When we seek to ascertain the causes of the morphological changes which result from the influence of the parasite on its host it is difficult in the present state of knowledge to find any very definite explanation. Localized growth is ordinarily a factor of differentiation, but here it has no reference whatever to that process. Davenport in his admirable treatise on experimental morphology has given a very clear discussion of the factors in the effect of chemical and physical agents upon growth, and has brought together the evidence which shows the acceleration of growth by contact, by cutting and by chemical stimulus. Now an examination of the cases in which growth is induced by parasites leads to the conviction that neither contact nor cutting can be a stimulating factor, since there are too many cases of parasitism in which no growth is produced, while in the exceptional case the presence of the parasite stimulates considerable growth activity. To be sure, it has already been suggested that the formation of a cyst about a resting parasite is a normal activity of the host and occurs very generally if not universally. This may be the result of a contact stimulus; it may also be explained on the same basis as the other cases, viz., as a result of chemical stimulus. Under the discussion of the acceleration of growth by chemical stimulus, Davenport says: "It is clear from this table that the addition of even small quantities of innutritious and poisonous substances may so affect the hylogenic processes as to cause twice or even far more than twice the normal formation of dry substance in a given time, and that this excessive growth increases with the concentration of the poisonous substances up to a certain optimum beyond which growth declines again to below the normal."

In suggesting that the stimulation of growth by parasites is traceable to chemical stimulus, and that the stimulating substance is a poison, I am advancing a hypothesis which, even though it is a purely tentative one, may well engage our consideration for a moment. Each parasite in the course of its activities produces a certain amount of waste material. It may

safely be affirmed that this substance, which in the case of a resting parasite must be discharged directly into the tissue of its host, is to that tissue poisonous. If such material is given off in small amount it will evidently act as a stimulant upon the surrounding cells and be the factor in bringing together the leucocytes which accumulate about the invading organism. An inert body of the same size, if introduced into the same position, would not induce the formation of a cyst or certainly the tissue proliferations which accompany in some cases the attacks of parasites. It may even be doubted whether under the conditions for pearl formation, grains of sand, as formerly believed, will give the proper stimulus for the formation of the pearl. The important factor then must be one which is associated with the organism, not as an object occupying space, but as a living thing, and the most evident characteristic of this is the giving off of waste matter. This leads naturally to the next subdivision of the subject.

As physiological effects may be grouped together those influences of the parasite on the host which express themselves in the limitation or modification of the normal physiological processes of the latter. In some cases it is often true here that the primary effect is hidden and that the secondary result alone can be seen. It is sometimes possible to determine the primary result by study of the secondary, and to see the way in which it has been brought about. In other cases we merely know the secondary effects without being able to disentangle from the complicated series of phenomena the primary cause. Furthermore, those interferences with normal function which are grouped under this heading are not such as might be traced to the action of the parasite as a foreign body, but such as are related to its own activity as a living organism. It will be seen that the distinction here is not perfectly clear, and perhaps somewhat artificial, for the mechanical disturbances of parasitism interfere with the normal activities of the host in the same way that other foreign bodies may modify or limit the working of the same organism. However, it is my intention under this heading to consider the results which come from the contact of life with life, the interaction of function with function.

Perhaps the most evident factor and the most frequently mentioned, certainly the first to be noted in this connection, is the absorption of nutriment. The parasite demands a certain amount of food matter to carry on its own vital processes. This food matter is furnished, so far as endoparasites are concerned at least, in a partially or fully digested condition, by the host animal. Many observers have maintained that the actual loss to the host in this way is so slight as to be negligible.

Leuckart says that a *Dibothriocephalus latus* 7 meters in length weighs 27.5 grams, and gives off in a year a total of 15 to 20 meters of proglottids of a weight of approximately 140 grams, and that *Tænia saginata* produces daily on the average 11 proglottids, an amount equal to about 550 grams. These figures have been taken by some to indicate the actual loss of food material on the part of the host; this would be evidently insignificant in comparison with the amount consumed by a man within the year. It has even been suggested that the increased appetite induced by the presence of the parasite more than compensates for this slight loss. It would appear, however, that such a method of statement is exceedingly inadequate. It is very difficult to estimate the amount of food consumed by an animal in proportion to its weight, but it is certainly grossly insufficient to indicate this in any way as commensurate with the amount of growth

which the animal achieves within a given period.

There is also another factor which must be taken into account, viz., that the parasite consists almost exclusively of actively functioning organs, and that there is a minimum of such inert parts as skeletal structures which add greatly to the weight of an animal, but do not involve the consumption of food material for their maintenance. It has been shown recently that parasites contain a large amount of glycogen; in analyses from one fourth to one third of the dry weight consists of this material. The highest value previously known was 14 per cent. in *Cardium* (a mollusk) and mammals apart from the liver have only about 3 per cent. Later the same author (Weinland) demonstrated that the vital processes of *Ascaris* proceed without oxygen and involve a fermentation process, resembling that of bacteria and yeast in producing butyric acid and alcohol. The possibility of such a wasteful process, measured in calories actually used, is found in the especially favorable conditions of existence of the parasite, which afford it carbohydrates in superabundance and both protection and warmth from the host. But naturally the waste of the process means draft on the host.

Furthermore, the presence of the glycogen, which is unquestionably reserve material, indicates unmistakably that metabolic processes are exceedingly active in the organism. Another indication of the same thing is to be found in the reproductive activity. The tapeworm is producing and maturing an enormous number of eggs, each of which is supplied with a considerable yolk dowry. It is safe to affirm that during reproductive periods the draft of any animal upon its food supply is at a maximum. All of these three items, then, the rapid growth of the individual, the production of an unlimited supply of reserve material and the extreme reproductive activity, point to a heavy draft upon the host. I have been unable to find any calculations which might be applied to such organisms as parasites with any likelihood that they would yield even approximate estimates of the material actually consumed. It would seem clear that previous calculations are incomplete and that the draft on the host is far greater than has been imagined heretofore.

An important effect on the host is traceable to the increase in the size of the parasite. This normal accompaniment of growth is most significant when the parasite occupies a limited space or when the increase in size is marked. The brain cysticercus, ordinarily found in a ventricle, grows until the cavity is occupied and then pressure upon the nervous tissue brings a sudden end to the life of the host. A liver hydatid may continue to grow almost without limit and only when important structures become involved is the pressure of serious moment. Most bladder worms do not exceed insignificant limits in growth and consequently exert little or no influence on the host. The echinococcus, through its indefinite growth, is sure to reach a size which will interfere with the activity of the host, and from its usual location in the liver is likely to include important vessels, or nerves, and lead to fatal interference with normal functions.

Another general influence which parasites are thought to exercise on the host is explained by the hypothesis of reflex nervous action. According to this view intestinal parasites affect the host by irritating the nerve terminations and provoking in reflex fashion the varied troubles of helminthiasis which the clinician recognizes. This is a rôle which has been regularly ascribed to them and yet, as Guiart says, this view is in fact a pure hypothesis. It has been invoked as an easy way to explain

the results of parasitism, and though attractive by its very simplicity, no evidence has been elucidated in its support, while at the same time many grounds have been advanced for other views. Accordingly, it is my intention to pass this hypothesis with the mere mention.

It has been frequently noted that parasitic infestation tends to retard the development of the host organism. In fact it does not hinder the general growth of the host strikingly, but arrests primarily its sexual development. This has been especially investigated by Alfred Giard, who denominates the phenomenon parasitic castration and defines it as the sum total of modifications produced by a parasite on the reproductive apparatus of its host, or on the portions of the organism indirectly in relation with that apparatus. The phenomenon appears to be wide-spread, instances being found in all branches of the animal kingdom and as the result of the most varied sorts of parasites. The character of this influence becomes evident through a simple comparison.

When an organ acquires undue importance one of the first physiological results of its hypertrophy is the arrest of sexual reproduction. Similarly when a parasite develops in an organism it causes sterility in its host. Such parasitic castration may be direct or indirect. The first case is met when the parasite destroys directly by mechanical means, or for its nutrition, the genital glands of its host. Parasitic castration is indirect when the producing parasite is not directly in relation with the genital glands, but in some other part of the body of the host. Parasitic castration may also be temporary and then disappear when the parasite is suppressed.

The modifications caused by parasitic castration affect the genital organs, the secondary sexual characters and the sexual instincts of the infested animals; it may be partial to any degree and may exert the same influences on the secondary sexual characters as age or as artificial castration. Each one of the sexes loses more or less its characteristic attributes and tends to acquire in the same degree those of the opposite sex. Thanks to the effective labors of Professor Giard, this phase of the influence of parasites on the host is more carefully worked out in comparative fashion than any other in the entire category. However, it would be clearly impossible within the necessary limits of this address to present the mass of evidence which he has collected from all parts of the animal and plant kingdoms.

A change which is mechanical to a certain extent and yet which has results of far deeper character, is the destruction of tissues by such parasites as actually feed upon the cells of the host animal. This is evidently due to the functional activity of the parasite and for that reason will lie outside of the limits of a purely mechanical process and may be considered here. Schaper has shown that the liver fluke (*Fasciola*) feeds upon the substance of the organ in which it lives. Now this destruction of liver tissue removes from functional activity a certain portion of a most important organ. In addition to that it is followed by a growth of connective tissue, so that there is a permanent loss in the functional activity of the organ. Many different kinds of alimentary parasites actually feed upon the wall of the canal, with the result that by the feeding and burrowing of the parasites through the mucosa this important structure is destroyed over considerable areas; the wall of the canal comes to be covered with ulcers and suffers at these points permanent functional injury. The serious secondary effects in such cases have already been noted and they are evidently not in any sense directly proportioned to the extent of the injury, but the

primary effect upon the functional process of the organ is directly related to the number of such injuries, or, in other words, to the number of parasites at work. Other parasites burrow into the intestinal wall and produce there nodules of various sorts. Nematodes particularly determine the formation of such nodules in various organs of the host.[5] These nodules may be of considerable size, but in any event they involve the destruction of some functional tissue and the consequent impairment of the functional activity of the organ.

Among the physiological activities of parasites none is more striking in its reaction upon the economy of the host than the power that has been acquired by some forms which live upon blood to secrete a substance that inhibits the coagulation of the blood. Leo Loeb and Smith have recently shown that the hook worm secretes in glands of the anterior body region a substance which is exceedingly effective in inhibiting the coagulation of blood. This is antagonistic to the normal reaction of the mucosa. Consequently the points at which these parasites have attached themselves to the membrane become seats of continued hemorrhage, and in case of a numerous infection by the species there are myriads of minute hemorrhages constantly discharging blood[6] into the cavity of the canal. The powerful anemia which is associated with the parasitism of the hook worm receives in this way a ready explanation.

There are many cases in which production of diseased conditions in the host appears distinctly traceable to the presence of a parasite and removable by the removal of the parasite. These diseased conditions are general, not local. They are apparently due to some abnormal stimulation and have usually been explained on the basis of the influence of toxic materials which the parasite produces. That parasitic organisms, like all other animals, produce waste matter and give it off into the fluids by which they are surrounded is not open to question. If the view already advanced of the active metabolism carried out by the parasites, and if the extremely highly developed excretory system are correct indications, then the amount of such waste material eliminated would be proportionately large. It is also undoubtedly true that various investigators have been able chemically to isolate toxic principles from the bodies of various parasites, and that in a number of instances these substances have been tested in their effects on living organisms with the result of producing changes or invoking symptoms distinctly analogous to those which have been recorded as the consequences of infection by the specific parasite. It also appears that the evidence which has been collected heretofore seems to indicate a difference in the degree of the effect exercised by living and by dead helminthes, for the latter are much more

[5] Thus *Sclerostoma equinum* produces tumors on the intestinal lining of the horse; *Spiroptera megastoma* in the submucosa of the horse; *Spiroptera sanguinolenta* in various organs of the dog, fox, etc.; *Œsophagostoma columbianum* in the intestine of sheep; *Strongylus Ostertagi* in the fourth stomach of cattle; *Gnathostoma siamense* in the subcutaneous tissue of man.

[6] As a matter of fact Looss has demonstrated that blood is not the normal food of the hook worm, as these parasites feed on the mucous membrane of the host, and blood is sucked in only when the parasite accidentally pierces a vessel. Looss takes the position that a toxin is produced which acts hemolytically, pointing out the fact that in some fatal cases of severe anemia the number of parasites found in the intestine was too few to explain the severity of the illness. It does not seem to me to be necessary to infer the production of some unknown toxin, since the possession of a secretion inhibiting the coagulation of the blood would account for the persistence of the hemorrhages, and it is this factor of continuance which makes of them dangerous elements. It is well known that the leech also produces such a substance in its glands.

dangerous than the former; and yet it should be remembered that our precise knowledge of these matters is exceedingly limited. The production of a substance by extraction from a parasite is not sufficient evidence that the animal actually eliminates this material. It may be that in the final step of elimination there are changes which radically alter the character of the substance, and that consequently there is under natural conditions no such material in position to act upon the host individual. It should also be remembered in this connection that the parasites are generally located in those organs into which waste is normally eliminated and by which it is discharged from the body; and, furthermore, that the parasitic organism sets free but a small amount of such waste material at any one time. These conditions would appear to indicate a minimum effect upon the host, if, indeed, any such existed.

On the other side, there are also certain incontestable facts. Not only is the recovery of such toxic substances from parasitic organisms by chemical means undoubted, but also it is known that as a result of injury or surgical intervention when a hydatid cyst is ruptured and the liquid content is diffused through the body, there are absorbed from it toxic substances which provoke serious results. Normally, the bladder worm is surrounded by a cuticula which retards osmosis, so that only a negligible quantity of toxin can be dispersed, while the rest is accumulated in the vesicle.

Another argument which has been advanced to question the actual relation of these toxic substances to the pathological conditions of the host is the great amount of variability in different cases, not only as between the effect of different parasites which would naturally be explained on the basis of different types of toxic substance, but also with regard to the effect of the same parasite in different cases. Now this may easily be due to individual susceptibility on the part of the host animal, but there is another feature which would go far towards explaining this variable effect and yet it has never been suggested in this connection. Under certain conditions an animal will absorb toxic substances from its own alimentary canal and induce diseased conditions within itself as a result of this perverted function. The application of the same principle to the case of parasites would account for the absorption of toxic materials by one host and their elimination in another case.

So far as the protozoa are concerned, the evidence is positive that in some cases toxic materials are the cause of the effect produced by the parasite. Thus the Hemosporidia of malaria undergo their development within the red blood corpuscles, and at the time of breaking up into spores the corpuscle is destroyed and the accumulated toxic material set free in the blood. Since the phenomena are synchronous for a large number of the parasites the amount of toxic material set free at once is considerable and is followed immediately by a febrile reaction, the periodicity of which is related to the successive reproductive cycles of the parasite.

The case of the Trypanosomes which are the cause of sleeping sickness is less definitely demonstrated, but apparently of the same type. In this disease no pathogenic changes can be observed in the host save a slight inflammation of the vascular membranes surrounding the spinal cord and brain. The toxins which the organisms in the spinal fluid produce must be set free in this fluid and thus act directly upon the central nervous system with the lethal effect characteristic of the disease. The result here is certainly not morphological and is satisfactorily explained on the basis of the production of a deleterious chemical stimulation.

But little is known regarding the chemical character of the substances under dispute. The indefinite idea that some toxic substance is produced has been replaced in one or two instances by a definite idea regarding the material and its manner of working. Such is the case in hook-worm disease, already discussed, and it may be that more extended study will furnish clearer ideas with regard to other cases. Some observers have determined the substances obtained extractively as leucomaines, while in other cases they have been found to be more nearly like enzymes. Certain of them react upon the blood with marked hemolytic power, while others of the ferment character affect nerve centers. An alkaloid which arrests muscular action has also been isolated.

The most difficult case to explain on any other theory than that of the production of toxic principles is the progressive, pernicious anemia, present in some cases of bothriocephalid infection. In spite of numerous investigations the case still remains obscure, but apparently one must admit that at least in special instances this parasite does excrete a particularly active toxin having hemolytic properties. Undoubtedly, the production of toxins by bacteria leads us to expect similar substances in this case also, but the argument from analogy is a dangerous one in scientific demonstrations. Perhaps the strongest argument in favor of the view that parasites produce toxic substances is to be drawn from the occurrence of eosinophilia, which will be considered next.

Among the white blood cells are such as from the affinity of their granular contents for certain stains are known as eosinophile cells. They constitute from 2 per cent. to 4 per cent. of the normal leucocyte count, and an absolute increase beyond the normal number of 250 per cubic millimeter is designated eosinophilia. The conditions which produce an eosinophilia vary so widely that the cells have been termed the most capricious element of the blood. To a certain extent this seems true of the many varied reports of parasitic invasions on record, as some observers in the case of almost every species record the absence of any eosinophilia. Yet evidence is growing that eosinophilia is a strikingly constant symptom of infections with animal parasites, and experiments on lower animals as well as the most careful and extended observations on man are nearly uniform in their testimony to the existence of abnormal numbers of eosinophile cells in the blood.[7]

Some authors indicate what may be the explanation of the negative results of other observers. Thus Calvert noted in cases of *Filaria Bancrofti* that the development of the eosinophilia followed a cyclical course, being more marked when the embryo round worms are absent from the peripheral blood and decreasing as the embryos increase these. The percentage of eosinophiles varied in one case from 3 per cent. to 15 per cent. during twenty-four hours. The observation has been confirmed exactly by Gulland, while other observers record similar or greater variations, though the minimum figures are higher. In fact, such fluctuations seem characteristic not only for this parasite, but also of most other species. In some cases the eosinophilia does not make its appearance at the first of the infection, and after a marked increase subsequently declines or even disappears as the disease becomes chronic. A reappearance of the eosinophilia and also irregular fluctuations in it during the course of the

[7] Thus tapeworm infection, hydatid cysts, the Egyptian blood flukes, and many other parasites, are associated with an increase in eosinophile cells in the blood. In trichinosis it is the rule and in hook-worm disease the main feature of the blood is an eosinophilia both relative and absolute.

malady are also noted. Such variations have been recorded in infections with tapeworms, with hook worms, with trichinæ and with various filariæ. To what extent predisposition and immunity influence the phenomenon can not be judged at the present time, owing to insufficient data and incomplete observations.

Equally characteristic with these fluctuations one must regard also the excessive degree of eosinophilia in parasitic diseases. While under other conditions an eosinophilia of 7 per cent. to 10 per cent. is usual, with rare instances of 35 per cent. to 50 per cent., in infections with animal parasites 10 per cent. to 30 per cent. is the average and 70 per cent to 80 per cent., or even 87 per cent., the extreme. The number of cases with such high percentages is large, even though the records in general are not numerous, indicating even more distinctly the usual character of the exceptional eosinophilia in such cases.

The intimate relation of the eosinophile cells to the parasite is strikingly indicated by two well-established facts. The first already referred to is the increase and decrease of these cells in the peripheral blood as the embryos of *Filaria Bancrofti* appear in the superficial capillaries and disappear from them. The second was established by Opie experimenting with trichina on guinea-pigs. The increase in eosinophile cells does not begin until the embryos start to migrate and reaches its maximum when the majority of the embryos are in transmission from the intestinal mucosa by way of the lymphatic vessels and the blood through the lungs to the muscular system. Sabrazes also found a great accumulation of eosinophile cells in the vicinity of hydatid cysts. All these facts would seem to indicate not only a stimulus, probably chemical, inducing the multiplication of the cells, but also a positive chemotactic influence which led the cells towards the source of the stimulus. Since the stimulus originates from the parasites, the simplest explanation finds it in the normal emanations of the animal, which as waste matter may be classed under the general category of toxins.

Among the physiological effects of parasitism is listed prominently the production of a condition of deterioration in the blood known as anemia, involving changes in the red blood cells and in bone marrow. In certain cases it has been possible to indicate with some definiteness the cause, as in the hook-worm anemia, already discussed. External parasitism of blood-sucking species, such as leeches or fish lice (argulids) produces anemic conditions through direct appropriation of blood, and if the parasites become numerous, enough is withdrawn to cause the death of the host.

But after the elimination of these instances there remain others in which an explanation can not be given at the present time. The most striking example of such cases is that of the broad fish tapeworm (*Dibothriocephalus latus*) frequently associated with a severe form of pernicious anemia which, indeed, is given the name of a bothriocephalus anemia. Also *Oxyurias* and *Ascaris* have been found less frequently in connection with the same pathological condition, though the connection is not satisfactorily demonstrated. Now in all these instances the amount of departure from the normal may vary from a very slight anemia to the maximum degree, while in many cases there appears to be no such effect from the presence of the parasite. The condition is also distinguishable from pernicious anemia due to inherent causes in that it disappears promptly with the expulsion of the parasites. Experiments made with an extract of the *Dibothriocephalus* injected into various animals have been successful in some cases in producing an anemia, but in other cases have

failed. The reason for this anemia is not loss of blood, and equally contrary to known facts are the various hypotheses, based on the length of stay in the intestine, the predisposition of the host and the condition of the parasite. The view that it is due to a toxin seems at present least open to criticism.

The discussion which has been laid before you in this address involves many terms which are rarely used in zoological circles, and many animals which are perhaps equally unfamiliar. To the average zoologist parasitism is a *terra incognita,* if not a *terra evitata!* The biological problems it presents were among the very first to be indicated, but have not received their proportionate attention in the intervening years. Just now there seems to be awakened interest in the subject and the results of investigations in this field are most hopeful. The subject is one which really overlaps the boundaries of zoology and encroaches upon the field of physiology and of medicine also. Much fine work has been done on the medical side of the topic, but the best results there can not be reached without generous cooperation from this side also. It is eminently fitting in this place to recall the splendid researches on morbific Protozoa carried out by a zoologist on the faculty of Columbia University. There is urgent need for similar work on other groups that the medical investigator may be furnished with those morphological, physiological and biological data upon which the successful prosecution of his studies depends. The work of the zoologists, Howard and J. B. Smith, on mosquitoes made possible the scientific victories of American physicians over disease in Havana and New Orleans. The recognition of hook-worm disease as an important factor in American medicine came through the pioneer work of the zoologist, Stiles. The splendid investigation of Councilman and his confrères on smallpox was not complete without the work of a zoologist, Calkins. The triumphs of modern science are being won by cooperative efforts and these are nowhere more indispensable than in the study of animal life, so peculiarly and closely related is it to the progress of the human race. At no point, however, is the contact more intimate than here where the zoologist is called to join with the investigator in medicine in achieving the amelioration of man's physical condition and the suppression of disease.

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## SCIENTIFIC BOOKS

*The Wing Veins of Insects.* By Professor C. W. WOODWORTH. University of California Publications, Technical Bulletins, College of Agriculture, Agricultural Experiment Station. Entomology, Vol. I., No. 1, pp. 1–152, September, 1906. Contributions from the Zoological Laboratory of the Museum of Comparative Zoology at Harvard College, under the direction of E. L. MARK. No. 181.

Probably no animal organs have been so minutely compared externally as have the wing veins of insects. Comparison is so easy, so unhampered by preliminary technique, and the significant characters are so tangible and withal so useful, they are universally employed in defining both major and minor groups. There are probably no animal organs that are dealt with in a specific manner by so many workers in zoology. Therefore, when there appears a pretentious work that assumes to extend the knowledge and advance the theory of venation it attracts immediate and wide-spread interest.

Such a work is this recent one by Professor Woodworth. Its purpose is "to develop a theory that will serve for the interpretation of the facts that have been so richly accumulated" (p. 3) and "to establish a rational theory of venation" (p. 143). It aims to cover the whole field, discussing, in order, the